BIOINSPIRED CONCEPTS: UNIFIED THEORY FOR COMPLEX BIOLOGICAL AND ENGINEERING SYSTEMS

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Abstract

The overall long-term objective of our research is to develop mathematical and software infrastructure in support of post-genomics research in systems biology. One near-term objective articulated in this abstract centers on a deeper understanding of the organizational principles of biological networks. A distinguishing theme of this work is its focus on scalable methods of robustness and model (in)validation with data, as opposed to relying purely on simulation. In computability terms, if simulation is viewed as a way to attack the NP hard side of biological problems, our approach attacks the coNP side. Much of the success of reductionist biology has depended on creative individuals who draw biologically meaningful inferences from data and computation using small scale and informal reasoning. This type of inference was critical because the reductionist research program itself offered no systematic tools to deal with complexity, only with the component parts. Far from being dispensed with, this reasoning process and its biological content must be both formalized and made rigorous, systematic, and scalable as well, and ultimately teachable. This requires the development of new mathematics as well as algorithms and software.

A central goal of modeling and simulation is to connect molecular mechanisms to network function to questions of biomedical relevance. Unfortunately, many of the most critical questions involve events which are extremely rare at the individual cell level where the mechanisms act yet catastrophic to the organism. Thus simulation methods that may be adequate for studying generic or typical behavior are entirely inadequate to explore such worst-case scenarios, which with conventional methods are computational intractable. We are extending the best-practice tools and algorithms for robustness analysis that have become standards in engineering to models of biological relevance, which are typically nonlinear, hybrid, uncertain, and stochastic. This includes integrating formal inference methods from the previously fragmented theories in Computer Science with those of Control and Dynamical Systems. This involves deep mathematical challenges that parallel those for technological networks, for which we have made dramatic progress, and on which we are building new tools for systems biology.

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1 General Introduction and Background

Biological networks connect devices of enormous complexity and sophistication even at their molecular level into modular components for sensing, signal processing, communication, computation, and actuation. These components are further integrated into vast regulatory networks with layers of feedback. No one doubts the vast range of capabilities that a deep understanding of this biological complexity would enable, but beyond the need for improved experimental technology, and sophisticated bionformatics to manage the data such improvements would continue to yield, there is little consensus as to exactly what further must be done. We claim that the overwhelmingly greatest source of complexity and the least current understanding lies in the signaling, communications, and computation modules, and even more so in the feedback control systems that they comprise. The solution to the challenge of biological complexity may not be to fundamentally change the way in which current molecular biology research is done so much as to augment this research with a new way of thinking about the systems integration issue itself.

Despite its enormous success, the reductionist program provides a poor foundation for many new technical challenges. For example, the ubiquitous connectivity and flexibility of the Internet as observed by the user is taken for granted, as are the wires, chips, and displays that make up the hardware, but it is rare for nonexperts to be aware of the complex layers of protocols and feedback regulation that makes the Internet's flexibility and robustness possible. Until recently, there has been limited theoretical support for the study of the systems-level challenges in either internetworking or biology, and limited academic research. Nevertheless, for some time there has been a widely shared vision there could be universal features of complex systems that can transcend these reductionist decompositions [1, 2, 3], and provide a unifying integration. Sharp differences have arisen however with regard to exactly what those features are. We believe there is now a clear, compelling, and coherent path emerging from the striking convergence of the three research themes of biology, technology, and mathematics.

First, biologists have provided a detailed description of the components of biological networks, and many organizational principles of these networks are becoming increasingly apparent. Second, advanced information technologies have enabled engineering systems to approach biology in their complexity. We are developing new theories that elucidate these similarities that are comparable in depth and richness with those available for more traditional subdisciplines. While these share with their traditional counterparts many of the domain-specific assumptions that overcome the intractability of more general formulations, this progress has sharpened the mathematical questions that are relevant to these important application domains. Thus we have the beginnings of the first coherent, complete theoretical foundation of the Internet [4, 5, 6, 7, 8, 9], and have also been developing new theory and software infrastructure to support systems biology [10, 11, 12, 1, 13, 14]. We are making rigor-

ous and precise the notion that this apparent network-level evolutionary convergence within and between biology and technology is not accidental, but follows necessarily from the universal requirements of efficiency and robustness.

While the full consequences of the claimed convergence emerging from these two areas will take years to be fully resolved, an important message is now clear. The method of decomposing complex systems into vertical layers of varying complexity and scale, wherein each layer is further decomposed horizontally into modules, appears to be not only ubiquitous but necessary. It is neither an accident of evolution nor merely an artificial construct imposed by humans to make biology and technology comprehensible, although that may be a wonderfully serendipitous side-effect. Thus we do not advocate abandoning the reductionist program of decomposing complexity, but in managing the process more consciously and systematically. The disciplinary decompositions that exist may indeed be historical artifices, but the need for such decompositions is not. The key to creating an integrated approach to understanding, exploiting, and mimicking biological complexity is not to replace existing technologies, but to augment them with a more flexible and rigorous technology for decomposition and recomposition.

Finally, the mathematical foundation is being developed for a far more unified theory of complex systems that overcomes the intractability that forced the disciplinary fragmentation in the first place, and this is the most important development for this project. It is in retrospect unsurprising that a genuinely new science of complexity, particularly biological, would require equally new mathematics to answer basic universal questions such as: Is a model consistent with experimental data, which may come from extremely heterogeneous sources? If so, is it robust to additional perturbations that are plausible but untested? Are different models at multiple scales of resolution consistent? What is the most promising experiment to refute or refine a model? These questions are all naturally nonlinear, nonequilibrium, uncertain, hybrid and so on, and their analysis has relied mainly on simulation. Unfortunately, simulation alone is inadequate. One computer simulation produces one example of one time history for one set of parameters and initial conditions. Thus simulations can only ever provide counterexamples to hypotheses about the behavior of a complex system, and can never provide *proofs*. (In technical terms, they can in principle provide satisfactory solutions to questions in NP, but not to questions in coNP.) Simulations can never prove that a given behavior or regularity is necessary and universal; they can at best show that a behavior is generic or typical. What is needed is an effective (and scalable) method for, in essence, systematically proving robustness properties of nonlinear dynamical systems. The possibility of such a thing (especially without P=NP=coNP in computational complexity theory) is profound and remarkable, and it is the foundation of our approach.

1.1 The Organization of Biological Networks

One of our goals is to develop a theory of biological organization that exploits the features of evolution and robustness to constrain the search spaces in our analysis algorithms. Specifically, our computational methods for modeling from data, simulation, and robustness analysis need not solve arbitrary unstructured problems, which are certainly intractable, but only those that are biological meaningful. Biological systems at every level of organization are highly structured, far from equilibrium, persist there robustly despite fluctuations in their environment and their components, and have evolved to this highly organized state. This places constraints on biological organization that has some parallels in technology but none in the other sciences. Algorithms that exploit this organization can be almost arbitrarily more efficient and reliable than those that do not, but it requires a rigorous theory to connect the robustness and evolvability of biological networks, with algorithms for modeling and system identification, analysis, and simulation. All of our results so far are extremely encouraging, but are merely the beginning of what we believe is possible.

Our main effort on organizational principles is to identify the features of biological networks, as opposed to arbitrary sets of chemical reactions, that make automatic and scalable computational methods feasible, even when the computational complexity classes are worst-case exponential or worse. A smaller effort has been focused on additionally elucidating organizational principles to provide greater understanding of biological complexity. We want to help answer the question "what is all this complexity for?" [15]. This will have a huge impact on computation, but the results can go beyond that. In particular, our program could be viewed as thinking of biological networks as a kind of technological network built on the physical substrate of biochemistry, as opposed to, say, the CMOS VLSI and fiber optics of the Internet. Biological networks integrate controls, communications, and computing in a way that engineers are just beginning to understand in a deeply theoretical way, and we have had great success on the forefront of those efforts. By explicitly connecting the theoretical challenges in advanced technological and biological networks, there is the promise for substantial synergy, and there is strong evidence already that this approach will bring novel insights to both areas [16, 17, 18, 19, 20, 21, 22].

1.2 Robust yet fragile systems

An emphasis on scalable and provably correct analysis methods is not just for mathematical completeness, but is driven by a ubiquitous property of complex engineering and natural networked systems: they are *robust yet fragile (RYF)*. Complex networks can provide remarkable robustness despite large perturbations in their environments and component parts, but they can also be extremely fragile to cascading failure events triggered by relatively small perturbations. We experience various illnesses,

crashes due to software bugs, viruses, worms, and denial-of-services attacks, power glitches, security screenings, etc, as annoying but rarely catastrophic. Typically, our networks protect us. But cancer and other epidemics, chronic auto-immunity, market crashes, terrorist attacks, large power outages and fires, etc, remind us that our complexity has a price. Indeed, most dollars and lives lost in natural and technological disasters happen in the few largest events, while the typical event is so small as to usually go unreported.

Many current military technical visions convincingly suggests that network complexity can provide robustness and efficiency that ultimately greatly exceeds that of comparable brute force approaches. The ultimate challenge will not be to make this apparent in demonstrations and typical scenarios, but to avoid the rare but catastrophic failures that seem to inevitable accompany new levels of complexity. Unfortunately, the entire scientific enterprise of experimentation, modeling, and simulation of complex systems has been most successful at studying their typical or generic behaviors. Thus it should be no surprise that the rigorous study of the fragility of complex systems would require new methods.

That the intrinsically "robust yet fragile" (RYF) nature of complex systems [23, 24, 2, 17, 3, 25] has the computational counterpart of "dual complexity implies primal fragility" is a key feature of our approach. Practically speaking, this completely changes what is possible computationally. Organisms, ecosystems, and successful advanced technologies are highly constrained in that they are not evolved/designed arbitrarily, but necessarily in ways that are robust to uncertainties in their environment and their component parts. These are extremely severe constraints, not present in other sciences but essential in both biology and engineering. The most obvious feature is that their macroscopic system properties can be both extremely robust to most microscopic details yet hyper-fragile to a few, and this must shape both modeling and analysis, and the experimental process that it interacts with. If most details don't matter, most experiments are relatively uninformative. If a few details are crucial, then this is where both modeling and experiments must focus, but neither a purely top-down nor bottom-up approach can reliably find them.

Thus failure to explicitly exploit the highly structured, organized, and "robust yet fragile" nature of such systems hopelessly dooms any method to be overwhelmed by their sheer complexity. Technically speaking, we can now formulate a wide range of questions for very general dynamical systems under a common Lyapunov-type umbrella, converting them into statements involving semi-algebraic sets, polynomial (nonlinear) equations and inequalities. Proving such statements is still coNP-hard, but real algebraic geometry, semi-definite programming, and duality theory from optimization provide new methods to systematically exhaust coNP by searching for nested families of short proofs using convex relaxations. Not only can we search for short proofs systematically, but a lack of short proofs implies, by a generalization of duality, intrinsic fragilities in the question itself. This feedback from computation to modeling does not imply P=NP=coNP, which is unlikely, but rather that inference

problems within coNP lacking short proofs can be traced to specific and meaningful flaws in models or data for which resolution can then be systematically pursued. Note that this is a radical broadening of the numerical analysts notion of ill-conditioning, and involves mathematics from a variety of previously unrelated disciplines. Again, in retrospect, this should not be surprising, but it creates enormous challenges in both education and the review process.

Though this is all very new, these methods have already found substantial applications in networking, biology, physics, dynamical systems, controls, algorithms, and finance [26, 27, 28, 29, 30, 31, 32, 26, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43], and work on connections with communications theory is in progress and discussed in the technical details. A side benefit of a deepening understanding of the fundamental nature of complexity in a general sense is also a new and more rigorous explanations for long-standing problems in physics associated with complex systems[24, 29, 40, 41, 42, 43, 44, 45, 29, 46, 47].

1.3 Robust and Scalable Validation of Models Against Data

Simulation will always be a workhorse of systems biology, but it can be enhanced substantially if conjectures formulated using simulation can be proved rigorously. The linchpin of our proposed modeling system is the development and implementation of theoretically-sound methods for model validation. Although some existing software tools provide mechanisms for comparing a model's behavior to experimental data (e.g., Gepasi [48, 49]), the methods used to date have been ad-hoc, brute-force approaches that do not scale to larger models. The theoretical framework described later in this document represents an unprecedented opportunity to create a system for model analysis and validation and iterative experimentation for large-scale, stochastic, nonlinear, nonequilibrium, mixed continuous and discrete models with multiple time and spatial scales. The remarkable quality of the theory is that it can be used to prove conjectures for this difficult class of models such as "this model cannot fit the data, no matter what parameters we use" and "this model is robust no matter how parameters are varied." This is something that previously has not been possible except for much simpler models. Yet this, together with sophisticated robustness analysis methods, is exactly the capability needed in order to allow realistic biological models to be analyzed and related back to the experimental data to help answer the question, "What is the next experiment that would best differentiate between the current alternative hypotheses?"

We are relying on SOSTOOLS as a fouccation for the system identification and parameter estimation research, however this reliance is less than it might appear. Our SOS/SDP framework actually recovers as special cases essentially all of the standard methods, so the worst-case scenario is that it merely provide an integrated and unified method to access what might otherwise appear to be quite disparate methods. This

is not an aspect of our methods that we emphasize but it is an important element in our optimism about their potential. Perhaps more important is the converse, that we are suspicious of new methods that cannot capture gold-standard methods already in existence. Another important issue is that the SOS/SDP methods are the only candidates for a successor to linear programs in providing all the features of automation, scalability, duality, structure, and fragility to hard problem classes involving stochastic, hybrid, and nonlinear dynamical systems, in addition to reducing to linear programs in the special cases when it applies. These two features, plus the implementation in a MATLAB toolbox, makes SOSTOOLS unique. It also has the benefit that a large, diverse, and sophisticated research community spanning control and dynamical systems, hybrid systems, optimization, and many areas of pure and applied mathematics has recently begun to focus substantial attention in this area.

2 Technical Background

2.1 Sum of Squares Programming

Consider a given system of polynomial equations and inequalities, for instance:

$$\begin{aligned} f_1(x_1, x_2) &:= \quad x_1^2 + x_2^2 - 1 = 0, \\ g_1(x_1, x_2) &:= \; 3x_2 - x_1^3 - 2 \geq 0, \\ g_2(x_1, x_2) &:= \quad x_1 - 8x_2^3 \geq 0. \end{aligned} \tag{1}$$

How can one find real solutions (x_1, x_2)? How to *prove* that they do not exist? And if the solution set is nonempty, how to optimize a polynomial function over this set?

Until a few years ago, the default answer to these and similar questions would have been that the possible nonconvexity of the feasible set and/or objective function precludes any kind of analytic global results. Even today, the methods of choice for most practitioners would probably employ mostly local techniques (Newton's and its variations), possibly complemented by a systematic search using deterministic or stochastic exploration of the solution space, interval analysis or branch and bound.

However, very recently there have been renewed hopes for the efficient solution of specific instances of this kind of problems. The main reason is the appearance of methods that combine in a very interesting fashion ideas from *real algebraic geometry* and *convex optimization* [50, 27, 51]. As we will see, these methods are based on the intimate links between sum of squares decompositions for multivariate polynomials and semidefinite programming (SDP).

We will outline the essential elements of this new research approach as introduced in

[27, 52]. The centerpieces will be the following two facts about multivariate polynomials and systems of polynomials inequalities:

1. Sum of squares decompositions can be computed using semidefinite programming.
2. The search for infeasibility certificates is a convex problem. For bounded degree, it is an SDP.

We will define the basic ideas needed to make the assertions above precise, and explain the relationship with earlier techniques. For this, we will introduce sum of squares polynomials and the notion of *sum of squares programs*. We then explain how to use them to provide infeasibility certificates for systems of polynomial inequalities, finally putting it all together via the surprising connections with optimization.

2.1.1 Sums of Squares and SOS Programs

Our notation is mostly standard. The *monomial* x^α associated to the n-tuple $\alpha = (\alpha_1, \ldots, \alpha_n)$ has the form $x_1^{\alpha_1} \ldots x_n^{\alpha_n}$, where $\alpha_i \in \mathbb{N}_0$. The *degree* of a monomial x^α is the nonnegative integer $\sum_{i=1}^n \alpha_i$. A *polynomial* is a finite linear combination of monomials $\sum_{\alpha \in S} c_\alpha x^\alpha$, where the coefficients c_α are real. If all the monomials have the same degree d, we will call the polynomial *homogeneous* of degree d. We denote the ring of multivariate polynomials with real coefficients in the indeterminates $\{x_1, \ldots, x_n\}$ as $\mathcal{R}[x]$.

A multivariate polynomial is a *sum of squares* (SOS) if it can be written as a sum of squares of other polynomials, i.e.,

$$p(x) = \sum_i q_i^2(x), \quad q_i(x) \in \mathcal{R}[x].$$

If $p(x)$ is SOS then clearly $p(x) \geq 0$ for all x. In general, SOS decompositions are not unique. For example, the polynomial $p(x_1, x_2) = x_1^2 - x_1 x_2^2 + x_2^4 + 1$ is SOS. Among infinite others, it has the decompositions: $p(x_1, x_2) = \frac{3}{4}(x_1 - x_2^2)^2 + \frac{1}{4}(x_1 + x_2^2)^2 + 1 = \frac{1}{9}(3 - x_2^2)^2 + \frac{2}{3}x_2^2 + \frac{1}{288}(9x_1 - 16x_2^2)^2 + \frac{23}{32}x_1^2$. The sum of squares condition is a quite natural sufficient test for polynomial nonnegativity. Its rich mathematical structure has been analyzed in detail in the past, notably by Reznick and his coauthors [53, 54], but until very recently the computational implications have not been fully explored. In the last few years there have been some very interesting new developments surrounding sums of squares, where several independent approaches have produced a wide array of results linking foundational questions in algebra with computational possibilities arising from convex optimization. Most of them employ semidefinite programming (SDP) as the essential computational tool. For completeness, we present in the next paragraph a brief summary of SDP.

Semidefinite programming SDP is a broad generalization of linear programming (LP), to the case of symmetric matrices. Denoting by $\mathcal{S}^n$ the space of $n \times n$ symmetric matrices, the standard SDP primal-dual formulation is:

$$\begin{array}{ll} \min_X C \bullet X & \text{s.t.} \left\{ \begin{array}{l} A_i \bullet X = b_i, \quad i = 1, \ldots, m \\ X \succeq 0 \end{array} \right. \\ \max_y b^T y, & \text{s.t.} \ \sum_{i=1}^m A_i y_i \preceq C \end{array} \tag{2}$$

where $A_i, C, X \in \mathcal{S}^n$ and $b, y \in \mathcal{R}^m$. The matrix inequalities are to be interpreted in the partial order induced by the positive semidefinite cone, i.e., $X \succeq Y$ means that $X - Y$ is a positive semidefinite matrix. Since its appearance almost a decade ago (related ideas, such as eigenvalue optimization, have been around for decades) there has been a true "revolution" in computational methods, supported by an astonishing variety of applications. By now there are several excellent introductions to SDP; among them we mention the well-known work of Vandenberghe and Boyd [55] as a wonderful survey of the basic theory and initial applications, and the handbook [56] for a comprehensive treatment of the many aspects of the subject.

From SDP to SOS The main object of interest in semidefinite programming is quadratic forms, that are positive semidefinite. When attempting to generalize this construction to homogeneous polynomials of higher degree, an unsurmountable difficulty that appears is the fact that deciding nonnegativity for quartic or higher degree forms is an NP-hard problem. Therefore, a computational tractable replacement for this is the following: even degree polynomials, that are sums of squares.

Sum of squares programs can then be defined as optimization problems over affine families of polynomials, subject to SOS contraints. Like SDPs, there are several possible equivalent descriptions. We choose below a free variables formulation, to highlight the analogy with the standard SDP dual form discussed above. A sum of squares program has the form

$$\begin{array}{ll} \max_y & b_1 y_1 + \cdots + b_m y_m \\ \text{s.t.} & P_i(x, y) \text{ are SOS}, \quad i = 1, \ldots, p \end{array}$$

where $P_i(x, y) := C_i(x) + A_{i1}(x) y_1 + \cdots + A_{im}(x) y_m$, and the C_i, A_{ij} are given polynomials in the variables x_i.

SOS programs are very useful, since they directly operate with polynomials as their basic objects, thus providing a quite natural modelling formulation for many problems. Among others, examples for this are the search for Lyapunov functions for nonlinear systems [27, 57], probability inequalities [58], as well as the relaxations in [27, 51] discussed below.

Interestingly enough, despite their apparently greater generality, sum of squares programs are in fact *equivalent* to SDPs. On the one hand, by choosing the polynomials

$C_i(x), A_{ij}(x)$ to be quadratic forms, we recover standard SDP. On the other hand, as we will see in the next section, it is possible to exactly embed every SOS program into a larger SDP. Nevertheless, the rich algebraic structure of SOS programs will allow us a much deeper understanding of their special properties, as well as enable customized, more efficient algorithms for their solution [59]. Furthermore, as illustrated in later sections, there are numerous questions related to some foundational issues in nonconvex optimization that have simple and natural formulations as SOS programs.

SOS programs as SDPs Sum of squares programs can be written as SDPs. The reason is the following theorem: A polynomial $p(x)$ is SOS if and only if $p(x) = z^T Q z$, where z is a vector of monomials in the x_i variables, $Q \in \mathcal{S}^N$ and $Q \succeq 0$. In other words, every SOS polynomial can be written as a quadratic form in a set of monomials of cardinality N, with the corresponding matrix being positive semidefinite. The vector of monomials z (and therefore N) in general depends on the degree and sparsity pattern of $p(x)$. If $p(x)$ has n variables and total degree $2d$, then z can always be chosen as a subset of the set of monomials of degree less than or equal to d, of cardinality $N = \binom{n+d}{d}$. Consider again the polynomial $p(x_1, x_2) = x_1^2 - x_1 x_2^2 + x_2^4 + 1$. It has the representation

$$p(x_1, x_2) = \frac{1}{6} \begin{bmatrix} 1 \\ x_2 \\ x_2^2 \\ x_1 \end{bmatrix}^T \begin{bmatrix} 6 & 0 & -2 & 0 \\ 0 & 4 & 0 & 0 \\ -2 & 0 & 6 & -3 \\ 0 & 0 & -3 & 6 \end{bmatrix} \begin{bmatrix} 1 \\ x_2 \\ x_2^2 \\ x_1 \end{bmatrix},$$

and the matrix in the expression above is positive semidefinite.

In the representation $f(x) = z^T Q z$, for the right- and left-hand sides to be identical, all the coefficients of the corresponding polynomials should be equal. Since Q is simultaneously constrained by linear equations and a positive semidefiniteness condition, the problem can be easily seen to be directly equivalent to an SDP feasibility problem in the standard primal form (2). Given a SOS program, we can use the theorem above to construct an equivalent SDP. The conversion step is fully algorithmic, and has been implemented, for instance, in the SOSTOOLS software package, described in the next section. Therefore, we can in principle directly apply all the available numerical methods for SDP to solve SOS programs.

2.1.2 Algebra and Optimization

A central theme throughout convex optimization is the idea of *infeasibility certificates* (for instance, in LP via Farkas' lemma), or equivalently, *theorems of the alternative.* As we will see, the key link relating algebra and optimization in this approach is the

fact that infeasibility can *always* be certified by a particular algebraic identity, whose solution is found via convex optimization.

Ideals and cones For later reference, we define here two important algebraic objects: the *ideal* and the *cone* associated with a set of polynomials: Given a set of multivariate polynomials $\{f_1, \ldots, f_m\}$, let

$$\textbf{ideal}(f_1, \ldots, f_m) := \{f \mid f = \sum_{i=1}^{m} t_i f_i, \quad t_i \in \mathcal{R}[x]\}.$$

Also, given a set of multivariate polynomials $\{g_1, \ldots, g_m\}$, let

$$\textbf{cone}(g_1, \ldots, g_m) := \{g \mid g = s_0 + \sum_{\{i\}} s_i g_i + \sum_{\{i,j\}} s_{ij} g_i g_j + \sum_{\{i,j,k\}} s_{ijk} g_i g_j g_k + \cdots\},$$

where each term in the sum is a squarefree product of the polynomials g_i, with a coefficient $s_\alpha \in \mathcal{R}[x]$ that is a sums of squares. The sum is finite, with a total of $2^m - 1$ terms, corresponding to the nonempty subsets of $\{g_1, \ldots, g_m\}$.

These algebraic objects will be used for deriving *valid inequalities*, which are logical consequences of the given constraints. Notice that by construction, every polynomial in $\textbf{ideal}(f_i)$ vanishes in the solution set of $f_i(x) = 0$. Similarly, every element of $\textbf{cone}(g_i)$ is clearly nonnegative on the feasible set of $g_i(x) \geq 0$. The notions of *ideal* and *cone* as used above are standard in real algebraic geometry; see for instance [60]. In particular, the cones are also referred to as a *preorders*. Notice that as geometric objects, ideals are affine sets, and cones are closed under convex combinations and nonnegative scalings (i.e., they are actually cones in the convex geometry sense). These convexity properties, coupled with the relationships between SDP and SOS, will be key for our developments in the next section.

Infeasibility certificates If a system of equations does not have solutions, how do we *prove* this fact? A very useful concept is that of *certificates*, which are formal algebraic identities that provide irrefutable evidence of the nonexistence of solutions.

We briefly illustrate some well-known examples below. The first two deal with linear systems and polynomial equations over the complex numbers, respectively.

- Range/kernel: $Ax = b$ is infeasible $\Leftrightarrow \exists\, \mu$ s.t. $A^T\mu = 0$, $b^T\mu = -1$.
- Hilbert's Nullstellensatz: Let $f_i(z), \ldots, f_m(z)$ be polynomials in complex variables $z_1, \ldots, z_n$. Then,

$$f_i(z) = 0 \quad (i = 1, \ldots, m) \quad \text{is infeasible in } \mathbb{C}^n \Leftrightarrow -1 \in \textbf{ideal}(f_1, \ldots, f_m).$$

Each of these theorems has an "easy" direction. For instance, for the first case, given the multipliers μ the infeasibility is obvious, since

$$Ax = b \quad \Rightarrow \quad \mu^T Ax = \mu^T b \quad \Rightarrow \quad 0 = -1,$$

which is clearly a contradiction. The two theorems above deal only with the case of *equations*. The inclusion of inequalities in the problem formulation poses additional algebraic challenges, because we need to work on an *ordered* field. In other words, we need to take into account special properties of the *reals*, and not just the complex numbers.

For the case of *linear* inequalities, LP duality provides the following characterization (Farkas lemma):

$$\left\{ \begin{array}{rcl} Ax + b & = & 0 \\ Cx + d & \geq & 0 \end{array} \right. \text{ is infeasible } \Leftrightarrow \exists\, \lambda \geq 0,\, \mu \text{ s.t. } \left\{ \begin{array}{rcl} A^T\mu + C^T\lambda & = & 0 \\ b^T\mu + d^T\lambda & = & -1. \end{array} \right.$$

Although not widely known in the optimization community until recently, it turns out that similar certificates do exist for *arbitrary* systems of polynomial equations and inequalities over the reals. The result essentially appears in this form in [60], and is due to Stengle [61], and is called Positivstellensatz.

$$\left\{ \begin{array}{rcll} f_i(x) & = & 0, & (i = 1, \ldots, m) \\ g_i(x) & \geq & 0, & (i = 1, \ldots, p) \end{array} \right. \text{ is infeasible in } \mathcal{R}^n$$

$$\Updownarrow$$

$$\exists\, F(x), G(x) \in \mathcal{R}[x] \text{ s.t. } \left\{ \begin{array}{l} F(x) + G(x) = -1 \\ F(x) \in \mathbf{ideal}(f_1, \ldots, f_m) \\ G(x) \in \mathbf{cone}(g_1, \ldots, g_p). \end{array} \right.$$

The theorem states that for every infeasible system of polynomial equations and inequalities, there exists a simple algebraic identity that directly certifies the nonexistence of real solutions. By construction, the evaluation of the polynomial $F(x)+G(x)$ at any feasible point should produce a nonnegative number. However, since this expression is identically equal to the polynomial -1, we arrive at a contradiction. Remarkably, the Positivstellensatz holds under *no assumptions* whatsoever on the polynomials.

In the worst case, the degree of the infeasibility certificates $F(x), G(x)$ could be high (of course, this is to be expected, due to the NP-hardness of the original question). In fact, there are a few explicit counterexamples where large degree refutations are necessary [62]. Nevertheless, for many problems of practical interest, it is often the case that it is possible to prove infeasibility using relatively low-degree certificates. There is significant numerical evidence that this is the case, as indicated by the large number of practical applications where SDP relaxations based on these techniques have provided solutions of very high quality.

Degree \ Field	Complex	Real
Linear	*Range/Kernel* Linear Algebra	*Farkas Lemma* Linear Programming
Polynomial	*Nullstellensatz* Bounded degree: Linear Algebra Groebner bases	*Positivstellensatz* Bounded degree: SDP

Table 1: Infeasibility certificates and associated computational techniques.

Of course, we are concerned with the effective computation of these certificates. For the Positivstellensatz, notice that the cones and ideals as defined above are always *convex sets* in the space of polynomials. A key consequence is that the conditions in Posivstellensatz for a certificate to exist are therefore *convex*, regardless of any convexity property of the original problem. Even more, the same property holds if we consider only bounded-degree sections, i.e., the intersection with the set of polynomials of degree less than or equal to a given number D. In this case, the conditions in the P-satz have *exactly* the form of a SOS program! Of course, as discussed earlier, this implies that we can find bounded-degree certificates, by solving semidefinite programs. In Table 1 we present a summary of the infeasibility certificates discussed, and the associated computational techniques.

As outlined in the preceding paragraphs, there is a direct connection going from general polynomial optimization problems to SDP, via P-satz infeasibility certificates. Pictorially, we have the following:

$$\text{Polynomial systems} \Rightarrow \text{P-satz certificates} \Rightarrow \text{SOS programs} \Rightarrow \text{SDP}$$

Even though we have discussed only feasibility problems, there are obvious straightforward connections with optimization. By considering the emptiness of the sublevel sets of the objective function, sequences of converging bounds indexed by certificate degree can be directly constructed.

2.1.3 SOSTOOLS

SOSTOOLS [63, 64] is a free, third-party MATLAB toolbox for solving sum of squares programs. The functions implemented in SOSTOOLS are based on the sum of squares decomposition of multivariate polynomials [65], which can be efficiently computed using semidefinite programming [55]. SOSTOOLS was the result of the recent interest in sum of squares polynomials [66, 65, 67, 27, 68, 69, 51], partly due to the fact that these techniques provide convex relaxations for many computationally hard problems such as global, constrained, and boolean optimization [66, 69, 51, 70, 71, 72].

In addition to the optimization problems mentioned above, sum of squares polynomi-

als (and hence SOSTOOLS) find applications in several systems analysis and control theory problems, such as nonlinear stability analysis [27, 57, 73, 34], robustness analysis [27, 57, 34, 14], nonlinear synthesis [74, 75], and model validation [76, 14]. Some other areas in which SOSTOOLS is applicable are geometric theorem proving [77] and quantum physics [29].

Currently, sum of squares programs are handled by reformulating them as semidefinite programs (SDPs), which in turn are solved efficiently, e.g. using interior point methods. Several commercial and non-commercial software packages are available for solving SDPs. While the conversion from SOS programs to SDPs can be performed manually for small size instances or tailored for specific problem classes, such a conversion can be quite cumbersome to perform in general. It is therefore desirable to have a tool that automatically performs this conversion for general SOS programs. This is exactly where SOSTOOLS comes to play. It automates the conversion from SOS program to SDP, calls the SDP solver, and converts the SDP solution back to the solution of the original SOS program. At present, it uses another free MATLAB add-on called SeDuMi [78] as the SDP solver.

All polynomials in SOSTOOLS are implemented as symbolic objects, making full use of the MATLAB Symbolic Math Toolbox's capabilities. This gives to the user the benefit of being able to do all polynomial manipulations using the usual arithmetic operators: +, -, *, /, ^; as well as differentiation, integration, point evaluation, etc. In addition, this provides the possibility of interfacing with the Maple symbolic engine and library, which is advantageous.

The user interface has been designed to be as simple, easy to use, and transparent as possible. A user creates an SOS program by declaring SOS program variables, adding SOS program constraints, setting the objective function, and so on. After the program is created, the user calls one function to run the solver. Finally, the user retrieves solutions to the SOS program using another function.

SOSTOOLS is available for free under the GNU General Public License. The software and its user's manual can be downloaded from the SOSTOOLS website [79]. It requires MATLAB version 6.0 or later, SeDuMi version 1.05, and the Symbolic Math Toolbox version 2.1.2. SOSTOOLS can be easily run on a UNIX workstation or on a Windows PC. It utilizes the MATLAB sparse matrix representation for good performance and to reduce the amount of memory needed. To give an illustrative figure of the computational load, all the demo files that are distributed along with SOSTOOLS can be solved in less than 8 seconds by SOSTOOLS running on a PC laptop with a 933 Mhz Intel Pentium-III processor and 384 MBytes of RAM.

2.2 Stability Analysis Using Sum of Squares Programming

It is striking that there are now so many areas of research in which the Sum of Squares approach and positivstellensatz find application. Formulating the problem as the emptiness of a set is an important step, but this only involves algebraic inequalities. A natural question to ask is whether we can use the aforementioned tools to answer meaningful questions on models of complex biological systems, in other words whether the properties of a dynamical system can be inferred by constructing these proofs. Such questions may involve the functionality of the system, something that simulation alone cannot guarantee. In particular, the stability of the equilibria of a particular biological system may be of interest. The question therefore is whether positivstellensatz and the Sum of Squares decomposition can provide an alternative to simulation for nonlinear systems.

This problem is particularly important for biological systems, as the nonlinearities and their possible hybrid nature can not be neglected and the tools to date that use exhaustive simulations are doomed by computational complexity as the state dimension increases and the number of parameters increases. As an alternative to simulation, the concept of Lyapunov function can be used as a certificate for stability of the system. Let us consider a system $\dot{x} = f(x)$ which has an equilibrium x^*, with a neighborhood $\mathcal{X}$. Lyapunov functions, usually denoted by $V(x)$ are nothing but energy-like functions that have the following properties:

$$V(x^*) = 0, \tag{3}$$

$$V(x) > 0 \quad \forall x \in \mathcal{X} \setminus \{x^*\}, \tag{4}$$

$$\frac{dV}{dt} = \frac{\partial V}{\partial x}(x) f(x) \leq 0 \quad \forall x \in \mathcal{X}. \tag{5}$$

For example, think of the pendulum with friction; the sum of the kinetic and potential energy can serve as a Lyapunov function, in that at the point of rest, the energy is zero, is positive in any other configuration, and while the system evolves the energy is non-increasing, due to dissipation because of friction at the hinge.

Lyapunov functions are at the center of nonlinear systems analysis and design. When the systems under investigation are uncertain, they can also be parameterized appropriately to serve as a robust stability proof, i.e. a proof that the system is stable for all values of the parameters. A more general class of systems, such as systems with equality, inequality and Integral Quadratic constraints can also be tackled by constructing Lyapunov functions (see the Appendix for more details).

Let us turn back to the two Lyapunov properties, namely the positive definiteness condition on $V(x)$, i.e. $V(x) > 0$ and the negative semidefiniteness of its time derivative, i.e. $\frac{dV(x)}{dt} \leq 0$. These are essentially positivity properties. How about using the Sum of Squares decomposition to check them? This idea is indeed the step that opened up the way to an algorithmic analysis of nonlinear systems. People understood

that the conditions in Lyapunov's stability theorem were difficult to test and there was no constructive methodology to construct these functions, but it took a century to develop the theory necessary for the construction of these energy-like functions through the Sum of Squares decomposition algorithmically [27]. The fact that there might be parametric uncertainty or other types of uncertainty in the system can also be dealt directly; parameterized Lyapunov functions can be constructed in the same unified manner. We can now obtain information about the properties of the system further away from the equilibrium, that no linearisation procedure could provide us.

The construction of Lyapunov functions in some region of the equilibrium reveals estimates of the 'region of attraction' of it; Sometimes the presence of other equilibria render any statement we make about the system non-global; this implies the use of inequality constraints in the state-space, to restrict the construction of the Lyapunov function in some region around the equilibrium, a formulation that can be taken into account in a unified manner. In fact quite a lot of problems in nonlinear dynamical systems theory can now be answered algorithmically, such as hybrid, time-delay, stochastic etc.

What might be misunderstood is that the system vector field, i.e. $f(x)$ in $\frac{dx}{dt} = f(x)$ should be in a polynomial form, so that the Sum of Squares decomposition of polynomials can be used to construct the corresponding Lyapunov function. However it is always possible, through a series of changes of variables and recasting to put the system description into polynomial, plus a few 'constraints' that describe the new variables. While most biological systems have or can be approximated by polynomial descriptions, in many cases models have rational or fractional vector fields; they appear naturally with the use of Hill Functions to describe a reaction's velocity in the Michaelis-Menten sense. In this case the denominator of the system description has always the same sign, as otherwise one is faced with the unrealistic case of a system with a finite escape time. Therefore the quality of the vector field and its properties would not change if one multiplied out the vector field by its least common denominator, thus producing a system in polynomial form ready for analysis using the Sum of Squares decomposition. Virtually any problem that can be formulated with a finite number of polynomial equalities and inequalities fits in this framework. The theory that we developed is indeed unified in this sense, and in all that will follow all these concerns will find solution by resorting to a generalization of Lyapunov's stability theorem to systems with equality, inequality and Integral Quadratic constraints. Even hybrid systems can be dealt with directly in this same framework, and we will come back to this later. Also, the methodology used to cover the stiff dynamics of equations by IQCs can be extended to systems containing nonlinearities and the resulting system can still be analyzed using the sum of squares machinery.

Similar analysis using sum of squares programming has also been developed for hybrid systems. Stability analysis of switched and hybrid systems has been treated in e.g. [80, 81, 82, 83]. See also [84] for a recent survey of the field. The developments in this area have been amazing, but again have been restricted to the analysis of linear switching

events with simple switching rules, etc. One way of proving stability of switched and hybrid systems is by using piecewise quadratic Lyapunov functions [80, 82, 83], which are constructed by concatenating several quadratic Lyapunov-like functions across the discrete modes of the system. This approach is quite effective but in many cases it can be conservative. Nonetheless, by constructing polynomial and piecewise polynomial Lyapunov functions using the sum of squares techniques, the power of the method can be significantly amplified. The method generalizes previous analysis methods using quadratic and piecewise quadratic Lyapunov functions. Some features of the new approach are as follows. First, stability can be proven with a smaller number of Lyapunov-like functions, eliminating the need of refining the state space partition. Second, the method can be applied to systems with nonlinear subsystems and nonlinear switching surfaces. Finally, parametric robustness analysis can be performed in a straightforward manner.

2.3 Formal Methods for Reachability Analysis

It has been noted previously that biological processes are multiscale and stochastic. Simulation and analysis of complex models of this kind is quite challenging. We have also emphasized a need for modeling systems at different levels of abstraction. These different abstract models are represented in different mathematical formalisms. One particularly useful formalism for representing useful abstractions, especially for purposes of analysis and simulation, is that of hybrid systems, either deterministic, nondeterministic (uncertain), or stochastic (uncertain, with underlying probabilistic interpretation).

Hybrid systems incorporate both continuous-time dynamics and discrete elements. The continuous dynamics are given using time varying variables through differential equations. In the realm of biological process modeling, the discrete dynamics can arise in at least three different ways. First, abstraction and simplification of a continuous model can result in discrete dynamics. For example, systems that exhibit multiscale dynamics can be simplified by replacing certain slowly changing variables by their piecewise constant approximation. This is done when interest is in analyzing the system on a small time scale. Additionally, sigmoidal nonlinearities are commonly observed in biological data correlation and the corresponding models often use (continuous) sigmoidal functions. These can also be approximated by discrete transitions between piecewise-linear regions. A second source of discrete behavior is the presence of an inherently discrete process. For example, dynamics in the presence of small number of molecules are best described using discrete steps. Finally, faulty modes may also be modeled using discrete mode changes. For example, in normal conditions, the kidney does not excrete any glucose, but it starts excreting glucose if the level of glucose rises very high. This change can be captured using a discrete transition.

Uncertainties and stochastic behavior are common in biology. Rate constants and several other parameters in models of biological systems are determined using algorithms for determining minimal error curve fits for available data points. Parameter values obtained this way are "representative" values, they do not capture all observed behaviors. The actual value of the parameter is possibly stochastic in a given range. In many cases, we are interested in knowing about *all possible behaviors* of the system, rather than the behavior of the system assuming a representative value for the parameters. For example, when studying the effect of insulin injections on blood glucose concentrations, we wish to know all likely blood glucose concentrations that a human body may exhibit. In such cases uncertainties can be modeled using nondeterminism and the resulting model can be analyzed for all possible behaviors. Thus, at suitable abstract levels, biological processes are effectively modeled as nondeterministic, uncertain hybrid systems. These models can then be analyzed for safety properties, that is, properties about all possible behaviors of the system. In principle, safety verification or reachability analysis aims to show that starting at some initial conditions, a system cannot evolve to some unsafe region in the state space.

2.3.1 Techniques Based on Sum of Squares Programming

Recently, a set of techniques based on convex optimization and sum of squares methods has also been proposed for reachability analysis of nonlinear and hybrid systems [85, 86, 87, 88]. These techniques verify temporal properties such as safety (e.g., something bad never happens), reachability (e.g., something good can happen), and eventuality/liveness (e.g., something good will surely happen) using certain functions of states called barrier certificates and density functions [85, 87]. Not only can they be applied to discrete transition systems, because of their deductive nature the techniques can be directly applied to systems with infinite or even uncountable number of states, such as continuous and hybrid systems.

For a simple illustration, consider a continuous system $\dot{x} = f(x, d)$ where x is the state of the system taking its value in the state space $\mathcal{X}$ and d is a disturbance input taking its value in $\mathcal{D}$. In addition, consider $\mathcal{X}_0 \subset \mathcal{X}$ as the set of possible initial states, and $\mathcal{X}_u \subset \mathcal{X}$ as the set of unsafe states. Suppose there exists a barrier certificate, i.e., a differentiable function $B(x)$ satisfying the inequalities

$$B(x) \leq 0 \quad \forall x \in \mathcal{X}_0, \tag{6}$$

$$B(x) > 0 \quad \forall x \in \mathcal{X}_u, \tag{7}$$

$$\frac{\partial B}{\partial x}(x) f(x, d) \leq 0 \quad \forall x \in \mathcal{X} \times \mathcal{D}. \tag{8}$$

Then it is easy to see that the safety property holds, i.e., that for all possible initial state $x_0 \in \mathcal{X}_0$ and for all possible disturbance input there exists no trajectory of the system that goes from the initial set to the unsafe set. As another illustration, consider the same system but now assume that $\mathcal{X}_r \subset \mathcal{X}$ is a set of "good" states that

should be reached by the system. Assuming that $\mathcal{X}$ is bounded, then the existence of $B(x)$ satisfying

$$B(x) \leq 0 \quad \forall x \in \mathcal{X}_0, \tag{9}$$

$$B(x) > 0 \quad \forall x \in \partial\mathcal{X}, \tag{10}$$

$$\frac{\partial B}{\partial x}(x) f(x,d) \leq -\epsilon \quad \forall x \in (\mathcal{X} \setminus \mathcal{X}_r) \times \mathcal{D}, \tag{11}$$

where $\partial\mathcal{X}$ is the boundary of $\mathcal{X}$ and ϵ is a positive number, will prove the eventuality/liveness property, i.e., that for all initial state in $\mathcal{X}_0$ and under all possible disturbance the trajectory of the system will reach the target set $\mathcal{X}_r$ in some finite time. Systems with hybrid dynamics can be treated in an analogous manner. The idea here is simply to ask that during the discrete transition the value of $B(x)$ also satisfies certain non-increasing conditions, similar to what we have in (8) and (11).

It is obvious that simulation is of limited use to address the verification of safety or eventuality properties stated above. Since the state of the system is uncountable, verifying by simulation that the properties hold in all cases is never exact, simply because it is impossible to test all system behaviors. In fact, simulation alone may fail to uncover the existence of bad behaviors. Using barrier certificates and density functions to prove safety, reachability, and eventuality is analogous to using Lyapunov functions to prove stability. It eliminates the needs to run simulations, to explicitly compute the flow of the system, or to propagate sets of states. Another consequence of their deductive nature is that the techniques are applicable to nonlinear, uncertain, and constrained systems. Moreover, safety verification of stochastic systems can be handled by computing an appropriate barrier certificate which upper-bounds the probability of reaching the unsafe set [86]. In this case, a function $B(x)$ which is a supermartingale, i.e., whose evolution along time is non-increasing on the *average*, is used.

The conditions that must be satisfied by barrier certificates and density functions are formulated as convex programming problems. In addition to benefits in terms of computation, the duality structure inherent because of their formulation as convex programs also gives theoretical advantages. For example, a completeness statement in safety verification using barrier certificates has been obtained by exploiting this duality structure [88]. For continuous and hybrid systems whose descriptions are in terms of polynomials, sum of squares programming described in Section 2.1 provides a hierarchy of scalable algorithmic methods for computing barrier certificates and density functions, where at each level the computational cost grows polynomially with respect to the system size. The computation can be performed efficiently using semidefinite programming, for example using the software SOSTOOLS. Because of the possibility to use sum of squares programming for computing barrier certificates and density functions, the methodology seems to be more scalable than many other existing methods that can handle nonlinear continuous and hybrid systems. Successful application of the method for verifying the safety property of a NASA life support

system, which is a nonlinear hybrid systems with 6 discrete modes and 10 continuous states, has been reported in [89].

3 New Results and Challenges

3.1 Model/Data Comparison for Validation of Biological Models

The new sum of squares based methodology described in the preceding sections provides for the first time a systematic, scalable approach to robustness analysis and model invalidation for nonlinear and hybrid DAE systems, complementing modelling and simulation with a powerful proof infrastructure. While it builds directly on decades of research in robust control and dynamical systems, it represents a true watershed in these subjects. The models used previously are simple enough that ad hoc approaches are modestly effective, but even here the sum of squares formalisms are much more efficient and effective, and they scale to larger problems. Furthermore, we believe that all of the above methods could in principle be taught at the undergraduate level, potentially streamlining the teaching of much of systems theory and giving broad access to powerful tools.

3.1.1 The General Form of Data Collaboration: SBPriME

GRI-Mech and SBPriMEare the work of our colleagues Andy Packard and Michael Frenklach, who are collaborating with Adam Arkin (all at UC Berkeley) on the Alliance for Cellular Signalling (AfCS) modeling project. The AfCS is a large project funded by NIH that is providing us with a modern example of post-genomics biology research, and as such has been a major driver for the development of our tools. They are currently the most sophisticated users of SOSTOOLS in the biology community. The GRI-Mech approach that has been adopted for system identification in the AfCS modeling effort puts theory/models and data on the same footing. It does not change the way experimentation is done, but requires a different approach to analyzing even one's own observations and, as a consequence, places new standards on data reporting. In this approach, referred to here as SBPriME, measured data, its estimated uncertainty, and a model of the experimental system is treated as an assertion whose correctness depends on the suitability of the model and the reliability of the measured data. Taken together, the model and measurement constitute a (low dimensional) constraint in the "global" unknown parameter space. Specifically, only those parameters that are consistent with the model/measurement pair are possible values of the unknown parameters.

Formally, the reportable content of an experiment and modeling effort consists of

1. A model, M, which relates input signals, output signals, initial conditions, modeled unknown parameters, and modeled unknown disturbances in an implicit manner
$$M(u, y, x_0, \theta, d) = 0 \tag{12}$$
The form of M is often an ordinary differential or difference equation, derived from a combination of first-principles, conservation laws and additional expert-supplied assumptions.

2. A parameter set Θ, which captures the a priori information about parameter values as $\theta \in \Theta$

3. A disturbance signal set $\mathcal{D}$, which captures the a priori information about unknown disturbances as $d \in \mathcal{D}$

4. Data, the measured quantities $(u_{\text{data}}, y_{\text{data}}, x_{0,\text{data}})$

Together, these form a constraint on the parameter space, that implied by writing all the information in a "publicly" accessible manner

$$M, \quad (u_{\text{data}}, y_{\text{data}}, x_{0,\text{data}}), \quad \theta \in \Theta, \quad d \in \mathcal{D}. \tag{13}$$

A collection of these constitute a multitude of assertions about the joint parameter space encompassed by the individual assertions. One would like to do reasoning on this collection. For instance:

- Is the collection consistent? More specifically, is the set of unknown parameters which satisfy each the model/measurement assertions a nonempty set? If not, then something is wrong about the collection, invalidating at least one of the model/measurement assertions. Moreover, a proof (experiment list, math programming utilities) to illustrate the invalidation exists. As an example, in section 3.1.3 we illustate a class of uncertain, nonlinear dynamical systems for which this consistency question reduces to linear programming.
- Can several consistent assertions be collapsed (i.e., reduced) into a single assertion whose description is simpler than simply the collection from which it was inferred?
- Which model/measurement pairs have the most impact on the collection's (in)consistency? Answering this can flag assertions that are possibly incorrect, though self-consistent.
- Which model assumptions have the most impact on the collection's (in)consistency? We want to look for architectures that are both consistent and whose consistency is robust to certain variations. Answering the posed question will flag assumptions within assertions that the consistency is fragile with respect to.

- What is the tightest range of predictions about an additional process model (i.e., its quantity of interest) possible given that these predictions must be consistent with the collection?
- What is the utility of a hypothetical experiment to further knowledge regarding the system. In this framework, "what-if" questions can be posed and addressed.

Informally, we refer to these questions as *Model/Data comparison problems.* It is important to note that all of these questions lead to set-intersection questions, which can be posed as constrained optimization problems. The purely mathematical task of extracting desired information from all reported experiments is relegated to high-powered, scalable, global optimization algorithms described in section 2.1. In most cases, duality results yield "derivative"-like information as well. This may be used, somewhat heuristically, in order to quickly screen (from a long list) specific model/data comparison problems to more fully analyze.

3.1.2 Connecting with System Identification

Our approach shares characteristics with conventional system identification. The latter also treats parameterized models and the use of experimental data to better characterize model parameters. Identification typically involves assumptions regarding the noise properties of measurements and disturbances, and optimization of a cost function to decide a best (maximum-likelihood (ML), maximum a posteriori probability) parameter value based on these noise statistics, the experimental data, and an a priori distribution on the parameters. In addition, it computes estimates of the variances in this optimal parameter. Because of this probabilistic framework, notions of data/model invalidation are less crisp. By contrast, our approach can be thought of as deterministic and worst-case, tracking the feasibility of well-defined inequalities drawn from models and data. No attempt is made to characterize the distribution of the parameters; inferences are drawn from the set of parameters that are not invalidated by the model/data pair.

Although our numerical techniques take a deterministic approach to experimental errors and parameter uncertainty, the necessity for collaborative data processing (and software to support this) put forth in this proposal are equally relevant in this traditional identification setting. To properly account for coupled uncertainty between multiple experimental analyses, data must be shared and reasoned with in a single processing step. The sum-of-squares relaxations developed to solve the data/model comparison problem will also benefit the identification community by virtue of improvements in constrained global optimizations methodologies.

3.1.3 Specific Model Forms

An instance of the model/data comparison problem outlined in the previous section with a tractable solution follows. Consider a discrete-time model, with uncertain coefficients whose evolution is governed by

$$y_k = \sum_{m=1}^{N} \theta_m \, p_m(y_{k-1}, \ldots, y_{k-M}, u_{k-1}, \ldots, u_{k-M}) + d_k \tag{14}$$

The polynomials $\{p_m\}_{m=1}^{N}$ are known. The parameter vector θ and the disturbance sequence d are unknown. A priori information consists of linear inequalities for θ as well as for d,

$$A \begin{bmatrix} \theta \\ d \end{bmatrix} \leq b \tag{15}$$

Given a sequence of data (y, u) and initial values $(y_{-1}, y_{-2}, \ldots, y_{-M})$, the model/data comparison problem is to determine if there exists a parameter value θ and disturbance sequence d consistent with the apriori information (the linear inequalities in equation 15) such that the data is reproduced by the model, or to prove that no such combination exists.

The structure of the system in equation 14 yields a validation (and hence falsification) problem decided with linear programming. Consequently, all of the desirable properties of linear programming (robust solvability, duality theory, favorable computational growth with problem size, a well defined notion of ill-conditioning) translate to this model/data comparison problem. A simple alteration of the vector field so that it not linear in the parameters, completely changes the complexity of the model/data comparison problem. Consider

$$y_k = p(y_{k-1}, \ldots, y_{k-M}, u_{k-1}, \ldots, u_{k-M}, \theta) + d_k \tag{16}$$

The polynomial p is known. Again, the parameter vector θ and the disturbance sequence d are unknown and a priori information consists of (e.g.) the linear inequalities in equation 15. This problem is not decidable by LP, though can be attacked in a scalable manner by the more powerful analysis techniques available with SOS programming and the barrier certificate approach, described below.

3.1.4 System ID challenges

The basic concepts in systems ID are well-known but implementation in the context of our goals for biology leads to computational challenges that we have begun to address. There are several elements that must be combined to adequately treat these issues. First, parameters in biological and engineering models vary enormously in their impact on network-level phenotypes. In particular, circuitry is designed

or has evolved to be largely insensitive to large variations in many parameters but with extreme sensitivity to a few. This simultaneous coexistence of robustness and fragility is typical, and has tremendous benefits, though it apparently leads to some confusion. One consequence is that robust parameters (in the sense that they can vary widely with little phenotype) will typically vary widely experimentally, and even if they do not, are intrinsically hard to identify from input-output experiments on the intact network. This is well-known in control theory. Fortunately, it is also the case that it is less important that these parameters be known accurately, compared to "fragile" parameters. What is not trivial is having the entire toolset of modeling, analysis, and system ID work with uncertain parameters throughout without the need to ultimately assign exact values, since in any important sense there are no condition independent "true values" for these parameters. Thus our use of explicitly uncertain models throughout is crucial, as is the unique capability of our methods to provide versatile sensitivity and robustness analysis of stochastic, hybrid, and nonlinear dynamical systems.

It is possible that important (e.g. fragile) parameters are nonetheless poorly estimated from a given set of data, for any number of reasons, and the determination of the next high value added experiment requires several elements. One is the identification through local sensitivity or global robustness analysis that the range of parameter values that are unfalsified by data is inadequate for predicting phenotypes of interest. The next is to turn the system ID and model (in)validation tools backwards to identify new data that, based on current models and understanding, would be most informative. These all lead to constrained optimization problems which are not convex except in the most trivial cases. Our methods are aimed at solving these optimization problems in a scalable and automated way, and the use of duality-based methods are particularly useful in using the dual variables to evaluate sensitivities to primal constraints. We have extensive experience with these issues for engineering control systems and more recently in the context of methane combustion, but applications in biology are new and largely untried.

A serious difficulty to be overcome is that we currently rely on control engineers to be very sophisticated users of robust control and system ID tools and combine them appropriately in specific applications. While the individual steps may be systematic, the combination currently requires too much user expertise, and thus is not automated and only scalable in the hands of experts. Overcoming this is a major goal of our research, but progress will require iteration on biologically motivated problems.

It is often the case that biological/chemical/physical understanding can be used to identify those dynamical variables or other outputs whose measurement will be most useful in model refinement, model invalidation, and parameter estimation. One advantage of our methods is that they allow direct inclusion of modeling information from very heterogeneous sources through the use of a rich class of constraints on state variables and parameters. The major obstacle to using these methods are twofold. One is the computational complexity of the resulting analysis, and addressing this is

the centerpiece of our proposed research. The other is that even with sophisticated tools, biologists must be able to describe both their data and their other sources of understanding, which can come from very diverse sources, in mathematical terms on which automated inference can be performed.

An issue that can be a source of confusion is that even in the linear case and even when data is generated from a toy linear model, the parameters of that model cannot be recovered exactly in the presence of noise, except asymptotically. This is well-known, as are various results on the effect of the noise forcing on the convergence, the effects of unmodeled dynamics, etc. In the case where system ID is done with real data, the notion of "true parameters" really makes no sense. For both of these reasons, in our PrIMe system ID and model (in)validation framework we focus not on finding "true" parameter values but describing sets of unfalsified models. The framework inherits from robust control the ability to naturally handle unmodeled dynamics and varied noise models, and SOSTOOLS enables the systematic use of nonlinear models. These are all the most advanced state-of-the-art capabilities available. As importantly, this includes the specific sense that SOS/SDP methods recover as special cases many of the "gold-standard" algorithms that were previously available. PrIMe and SOSTOOLS thus form the foundation of our methodology. Nevertheless, we expect they will need to be extended substantially to scale to many problems of biological interest.

3.1.5 Blending Surrogate Model and Barrier Certificate Methods

The surrogate model approach is popular in chemical kinetics modeling, and has even been used successfully in the past 6 months to invalidate textbook models of calcium signalling using AfCS data. An important step of the method is to replace the dynamical model with a static model mapping the effect of the uncertain parameters to one specific feature of the dynamic model's response, under the action of one specific input and initial condition. This drastically reduces the complexity of the falsification step. Rather than dealing with dynamical models, the falsification step is faced with checking the emptiness of a collection of polynomial inequalities, which is adequately addressed using sum-of-squares optimization and the positivestellensatz theory address such inequalities.

The barrier certificate approach described in Section 2.3 works directly with the dynamical model, and is applicable to model validation of a rich class of dynamical systems. Note that this problem can also be treated as a reachability analysis problem. If a measurement indicates that the initial state of the system $\dot{x} = f(x)$ is contained in a set $\mathcal{X}_0$, whereas another measurement indicates that after some time the state is in $\mathcal{X}_u$, then the existence of $B(x)$ satisfying (6)–(8) will prove inconsistency between model and data, hence invalidate the model. Information on the measurement time can also be included in this analysis, by augmenting the state of the system with time. Applied to the special case in equation (14), for example, where LP is sufficient

to decide inconsistency, the barrier certificate approach will yield the same decision (conclusion) for linear barrier certificates satisfying some appropriate conditions.

Since a polynomial of a given order is determinable from a collection of its sample values, it is possible to interpret the barrier function method (and even do the computations, likely more numerically well-conditioned) as operating only with simulated data. Viewed in this vein, the surrogate model approach and the barrier function approach have similar starting points—families of simulations of the parametrized model over its parameter space. They differ in the use of this simulated data. One goal of this research for which we have had some limited initial success is to create a family of falsification methods, based on model simulations, that includes as a special case both the surrogate model and barrier function approaches.

3.2 Extending Methods for Reachability Analysis of Hybrid Systems

There have been in the past several independent approaches to the algorithmic analysis of hybrid systems, a challenge in both technological and biological networks. The combination of continuous and discrete dynamics presents a challenge for which very few good tools exists. Even in the case of purely continuous behavior, arguably much simpler, the computational perspectives seemed grim outside the linear case. Fortunately, in the specific case of the highly nonlinear hybrid systems arising in biological models, the introduction of the sum of squares based methodology has given renewed hope and many concrete examples, impossible to analyzed by other methods.

Clearly, what will be needed in order to extend the reach of the methods from our initial examples to medium and large-scale biologically and technologically relevant applications, is an intensive blend of the best elements of all successful approaches. In particular, as lessons from the computer science perspective, we extract the fundamental need of the use of hierarchies of abstractions to decouple the successive theorem-proving stages, as a way to deal with complexity. Such a strategy appears every time difficult problems are tackled, in domains ranging from pure mathematics to VLSI design. The first steps will be the simpler case where the hierarchies are designed in an ad-hoc fashion, and the algorithmic tools are used at each successive level of inference and theorem proving. Further down the road, we imagine to be able to use feedback from the dual solutions, to produce likely counterexamples and suggestions on possibly optimal decompositions. Furthermore, we expect the efficient exploration of proof space performed by the convex optimization algorithms in the SOS case is a novel concept for the theorem proving community, and one that we expect to be of benefit in some of the central tasks in other domains.

3.3 Analysis of Spatially Distributed Dynamics

The algorithmic analysis of spatially distributed systems has been in the center of scientific research for many years now [90, 91, 92]. Most techniques that are employed to understand their properties center on discretization of the describing Partial Differential Equation (PDE) and performing simulations on the resulting finite dimensional description. This technique is particularly useful when the domain of definition of the PDE is complicated. Our effort on this program will be twofold; first, we will develop a methodology to obtain estimates on functional outputs of the PDE, that can guide the choice of an adequate mesh size so that the simulation output will be representative of the PDE description. Secondly, we will consider common PDE systems on simple domains, aiming to answer analysis questions about them such as stability, model verification etc. The basis for the algorithmic technique is the sum of squares decomposition and SOSTOOLS.

The first issue we have tackled is related to the problem of estimating lower bounds on functional outputs of PDEs [93]. Such *a-priori* information is extremely useful for choosing the size of the discretisation required to capture the problem features in a CFD simulation. Mesh adaptivity and modern *a-posteriori* methods may not perform well in certain cases, and this is why *a-priori* methods are required. Using the results of model invalidation, there are two methods that can be applied to obtain such bounds. In the first one, model invalidation can be applied to an equivalent system that includes the output functional as one of the states; invalidating values that this new state can achieve provides estimates for the values of the output functional. The other method, which is essentially the dual of the first one, can be applied in the elliptic and parabolic case where the maximum principle applies; the solution is approximated by a polynomial and a series of upper and lower bounds can be achieved by solving an appropriately formulated sum of squares problem. The differences between the two methods is that the dual method can be used for PDEs in many dimensions but it cannot handle nonlinear functional outputs or other types of PDEs where the maximum principle does not apply, whereas the first approach can be applied in these cases, but is only for systems in one dimension. With an appropriate extension of the notion of barrier certificates to the notion of barrier functionals, we expect to be able to extend this to PDEs in many dimensions.

The second issue we have begun to address is related to analysis questions such as stability, model invalidation, etc. The standard analysis tools center on the construction of appropriate Lyapunov-type certificates. Several issues arise, such as the choice of the norm in which the analysis should be performed, but now the analysis can be done entirely algorithmically. Crucial steps in any analysis procedure for PDEs involve integration by parts of the candidate Lyapunov functional, establishing functional positivity, etc., for which we have well developed techniques. The difficulties involve choosing candidate structures and infinite-dimensionality of the spaces. We have most progress on infinite dimensional systems of a particular type: time-

delay systems. In this case, the so-called Lyapunov-Krasovskii functionals can been constructed algorithmically to prove stability of the equilibria [94]. Also, analysis of network congestion control schemes for the Internet, for arbitrary topologies, delays and link capacities has been successfully tackled [95, 96]. Moreover, results in this area have also been applied to nonlinear stability analysis of systems ranging from population dynamics to economics.

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Transitions
The SOSTOOLS software is now available free and open source. The SBML (Systems Biology Markup Language) has become a de facto standard in the systems biology research community.

New Discoveries
Unified theory using SOS methods for a large variety of problems relevant to systems biology and advanced technological networks, as detailed above.

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J. M. Carlson and J. C. Doyle. Complexity and robustness. *Proceedings of the National Academy of Sciences, USA*, 99:2538–2545, 2002.

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